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Table 1—Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

Drug/chemical	% binding to plasma protein	pK_a[a]	% un-ionized at pH 7.4	Permeability constant ($P\ min^{-1}$) ± S.E.
Drugs mainly ionized at pH 7.4				
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00005
5-Nitrosalicylic acid	42	2.8	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.005 ± 0.0004
Mecamylamine	20	11.2	0.016	0.031 ± 0.0016
Quinine	76	8.4	0.09	0.078 ± 0.0061
Drugs mainly un-ionized at pH 7.4				
Barbital	<2	7.5	55.7	0.026 ± 0.0022
Thiopental	76	7.6	61.9	0.50 ± 0.051
Pentobarbital	40	8.1	88.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.8	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.009 ± 0.0003
Antipyrine	8	1.4	>99.9	0.12 ± 0.013
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.018 ± 0.0010

[a] The dissociation constant of both acids and bases is expressed as the pK_a, the negative logarithm of the acidic dissociation constant.
[b] Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion*.

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Fig 9.

For the purpose of further illustrating the principle, Table 1 is provided.[7] In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine and acetylaminoantipyrine—may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through in order to gain access to the extracellular fluid, it might be expected that the particular site of application (or *route*) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

Routes of Administration

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, parenteral, inhalation and topical. The choice of a route depends upon both convenience and necessity.

Oral Route—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with gastrointestinal intolerance, or who are in preparation for anesthesia or who have had gastrointestinal surgery. Oral administration also is precluded in coma.

Rectal Route—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Fig 10[8] the availability of a drug by retention enema may be compared with that by the intravenous and oral route and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate where rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,[9] but, rather, to show that the retention enema may offer a useful substitute for the oral route.

Sublingual or Buccal Route—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations where a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

Parenteral Routes—These routes, by definition, include any route other than the oral-gastrointestinal (enteral) tract,

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10^{-3}

rical bars represent s.d. Δ 20–49 mean 73 years, n = 8).

levered the literature concerning n the sensitivity of animal aortae e evidence is conflicting. Cunlet urated a decrease in sensitivity n the rat. Gray (1977) found no ity with age in the dog while 78) found no change with age in these studies involved immature s as opposed to a comparison d senescent. The present study elderly subjects. There was no the sensitivity of human arterial aline. This is found when the ine is considered alone or when it non-receptor mediated contrac assium.

ries for these experiments had to ects with an underlying disease. to surgery, receiving medication adrenergic nervous system nor underlying arterial disease. Our ed by recent studies *in vivo* with eers (Elliot *et al.*, 1981) and with in young and old subjects).

an find no evidence *in vivo* that vascular α-adrenoceptor sensitivity increasing age. Further studies will ermine whether changes in β- a subtypes of α-adrenoceptors ardiovascular system.

BIOAVAILABILITY OF SUBLINGUAL ERGOTAMINE

Sublingual ergotamine has been used for years in the treatment of migraine attacks without any proof of its effectiveness. In a double-blind clinical trial no difference in relief was found between sublingual ergotamine and placebo (Crooks *et al.*, 1964). Similarly, a study on the buccal absorption of ergotamine indicated that it is unlikely for therapeutically useful amounts of drug to be absorbed across the buccal membrane (Sutherland *et al.*, 1974).

In contrast, Winsor (1981) in a nonblind cross-over study with finger-plethysmography found that the peripheral vasoconstrictory effect of ergotamine was equal after 0.25 mg intramuscularly or 2 mg sublingually, and significantly different from sublingual placebo. The two forms at these doses should thus be equally effective in migraine. With a high performance liquid chromatographic (h.p.l.c.) assay for ergotamine, with a detection level of 0.1 ng/ml in plasma (Edlund, 1981), we have investigated several administration forms of the drug. The results for sublingual ergotamine are reported as they cast serious doubt on the equipotency of sublingual and intramuscular forms of ergotamine.

Four volunteers (medical personnel, non-migraineurs) kept a sublingual tablet of 2 mg ergotamine tartrate (Lingraine®, Winthrop) under the tongue until dissolved. Blood was drawn after 5, 10, 20, 30, 60, 90 and 120 min. The samples were immediately centrifuged and kept deep frozen until analysed by the h.p.l.c. method. Ergotamine above the detection level was not found in any of the samples. Then the procedure was repeated in the same volunteers with another batch of Lingraine®. Again no ergotamine could be detected. The manufacturer informed us that both batches of Lingraine® were more than 2 years before their expiry date. For comparison we selected 4 migraine patients, who during the same period had their plasma levels of ergotamine determined with h.p.l.c. after 0.5 mg ergotamine tartrate/70 kg body weight intramuscularly. The mean and range of ergotamine levels in ng/ml plasma were after 30 min: 0.96 (0.48–1.41), after 60 min: 0.80 (0.57–1.07) and after 120 min: 0.57 (0.43–0.71). Even corrected to a dose of 0.25 mg the plasma levels of ergotamine are clearly above the detection level of 0.1 ng/ml.

These results were not obtained in a regular cross-over study. However, the discrepancy in plasma

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levels between sublingual and intramuscular ergotamine is so striking that it is unlikely for ergotamine 2 mg sublingually to have the same bioavailability as 0.25 mg intramuscularly.

Are the two forms of ergotamine then equipotent in their vasoconstrictory effect due to some active metabolites not measured by the specific h.p.l.c. method? Before going into speculations along these lines, we would suggest that the results with finger-plethysmography should be confirmed in a placebo controlled double-blind study with direct measurements of the vasoconstrictory effect of ergotamine. Our main objection against the results with finger-plethysmography is that the effect of the reference form, intramuscular ergotamine, only had a duration of 90 min on venous occlusion blood flow. This short duration of action is not in agreement with recent investigations on arteries with ergotamine (Tfelt-Hansen *et al.*, 1980) and on veins with dihydroergotamine (Aellig, 1981). The duration of these ergot alkaloids vasoconstrictory effect in man was found to be at least 24 and 8 h respectively. Further, a dose-response curve for the biological effect should be established before the question of biological equipotency can be answered satisfactorily.

If proven to be equipotent to parenteral ergotamine in such studies, sublingual ergotamine should undergo a controlled clinical trial in migraine.

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VERAPAMIL BIOAVAILABILITY AND DOSAGE IN LIVER DISEASE

May we be permitted to comment on the critical remarks made by Somogyi *et al.* (1981) on our dosage recommendations for verapamil and at the same time discuss the wider significance of verapamil dosage in liver disease.

Somogyi *et al.* (1981) recommend that the oral dose of verapamil in liver cirrhosis patients should be greatly reduced, and more so than required in the case of the intravenous dose. The oral dose they recommend is as little as one fifth of that used in patients with normal liver function. In our dosage recommendations, based on intravenous administration in patients with cirrhosis, hepatitis and fatty liver disease, a reduction to about one third was indicated, although there was considerable inter-patient variation (Woodcock *et al.*, 1979). Verapamil clearance data following oral treatment in liver patients were not available at this time. Somogyi *et al.* (1981) state that we 'failed to appreciate the difference between oral and intravenous clearance of verapamil' and thus imply that we were erroneous in the interpretation of our observations. This statement, apart from being incorrect (the first pass effect of verapamil is common knowledge since the report of Shomerus *et al.* (1976)) misses the fundamental point which is that the large reduction, to one fifth, in the oral dose of verapamil recommended by themselves, applies only to liver cirrhosis patients who have marked intra- and extra-hepatic shunts. This fact was omitted from their discussion.

We have reported observations on liver cirrhosis patients in whom the bioavailability of verapamil was the same as in healthy subjects despite a greatly reduced systemic clearance (Woodcock *et al.*, 1981). In patients with fatty liver the first pass extraction was increased and the bioavailability actually lower than normal. A higher than normal extraction of verapamil is, according to Wilkinson & Shand (1975), to be expected when the rate of blood flow through the liver is reduced. In these patients there was thus no evidence for the development of hepatic shunts and a dosage reduction of the magnitude suggested by